PCT WORLD INTELLECTUAL PROPE
International Bu

INTERNATIONAL APPLICATION PUBLISHED UNDER WO 9606070A1

(51) International Patent Classification 6 :
C07C 251/24, C07D 213/80, 215/38, 311/58, 311/70, 335/06, 333/38, 307/68, 215/12, A61K 31/19, 31/47, 31/38, 31/35, 31/34

A1

(11) International Publication Number: **WO 96/06070**

(43) International Publication Date: 29 February 1996 (29.02.96)

(21) International Application Number: PCT/US95/10802

(22) International Filing Date: 22 August 1995 (22.08.95)

(30) Priority Data:
08/294,901 23 August 1994 (23.08.94) US

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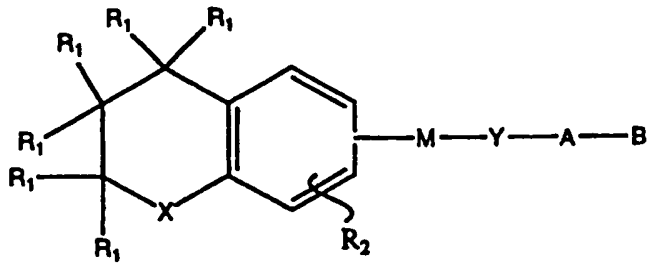
(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: DISUBSTITUTED ARYL AND HETEROARYL IMINES HAVING RETINOID-LIKE BIOLOGICAL ACTIVITY



(1)

(57) Abstract

Compounds of formula (1) wherein the R_1 groups independently are hydrogen, lower alkyl of 1 to 6 carbons, or two geminal R_1 groups jointly represent an oxo (=O) or a thio (=S) group; R_2 is hydrogen or lower alkyl of 1 to 6 carbons, or halogen; M is or -N=CR_4- or -R_4C=N- where R_4 is hydrogen or lower alkyl of 1 - 6 carbons; X is $C(R_1)_2$, O, S, or NR_1; Y is a phenyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pirimidinyl, pyrazinyl, thiazolyl, imidazolyl and oxazolyl, said phenyl group or said heteroaryl groups being optionally substituted with an R_3 group which is lower alkyl of 1 to 6 carbons or halogen; A is $(CH_2)_n$ where n is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds; B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, -CH_2OH, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, -COR_7, $CR_7(OR_{12})_2$, or $CR_7OR_{13}O$, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons have retinoid-like biological activity.

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DISUBSTITUTED ARYL AND HETEROARYL IMINES HAVING RETINOID-LIKE BIOLOGICAL ACTIVITY

1. Field of the Invention

The present invention relates to novel compounds having retinoid-like activity. More specifically, the present invention relates to compounds having an imine function which is substituted on the one hand with a 5,6,7,8-tetrahydronaphthyl, chromanyl, thiochromanyl or 1,2,3,4-tetrahydroquinolinyl group and by a substitutued aryl or substituted heteroaryl group having a carboxylic acid ester or carboxylic acid function. The acid function may also be converted to an alcohol, aldehyde or ketone or derivatives thereof, or may be reduced to $-CH_3$.

2. Background Art

Compounds which have retinoid like activity are well known in the art, and are described in numerous United States and foreign patents and in scientific publications. It is generally known and accepted in the art that retinoid like activity is useful for treating animals of the mammalian species, including humans, for curing or alleviating the symptoms and conditions of numerous diseases and conditions. In other words, it is generally accepted in the art that pharmaceutical compositions having a retinoid like compound or compounds as the active ingredient are useful as regulators of cell proliferation and differentiation, and particularly as agents for treating dermatoses, such as acne, Darier's disease, psoriasis, icthyosis, eczema and atopic dermatitis, and for treating and preventing malignant hyperproliferative diseases such as epithelial cancer, breast cancer, prostatic cancer, head and neck cancer

and myeloid leukemias, for reversing and preventing atherosclerosis and restenosis resulting from neointimal hyperproliferation, for treating and preventing other non-malignant hyperproliferative diseases such as endometrial hyperplasia, benign prostatic hypertrophy, proliferative vitreal retinopathy and dysplasias, for treating autoimmune diseases and immunological disorders (e.g. lupus erythematosus) for treating chronic inflammatory diseases such as pulmonary fibrosis, for treating and preventing diseases associated with lipid metabolism and transport such as dyslipidemias, for promoting wound healing, for treating dry eye syndrome and for reversing and preventing the effects of sun damage to skin.

United States Patent Nos. 4,980,369, 5,089,509, 5,162,546, and 5,175,185 disclose acetylene compounds which are substituted by a chromanyl, thiochromanyl or tetrahydroquinolinyl group and by a substituted phenyl or heteroaryl group, having retinoid-like biological activity.

United States Patent Nos. 5,013,744, 5,175,185 and 5,264,456 disclose acetylene compounds which are substituted by an alkylphenyl, alkoxyphenyl or thioalkoxyphenyl group and by a heteroaryl carboxylic acid or carboxylic acid ester group, having retinoid-like biological activity.

United States Patent No. 4,992,468 discloses diphenyl ethylene compounds having retinoid like biological activity. EPO patent application No. 0130795 discloses chroman or thiochroman and phenyl substituted ethylene compounds having retinoid-like biological activity.

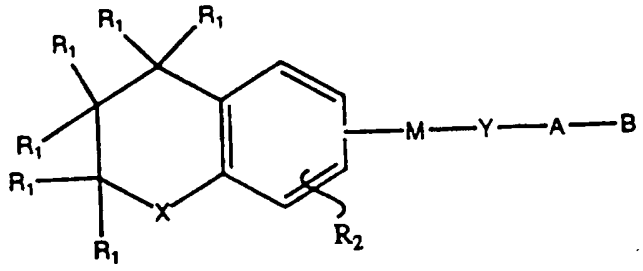
United States Patent Nos. 5,006,550, 5,015,658, 5,130,335, 5,143,159, and 5,231,113 disclose esters and thioesters of substitued phenol compounds (such as of para-hydroxy benzoic acid) with 5,6,7,8-tetrahydronaphthoic acid, chromanoic acid or thiochromanoic acid, having retinoid like biological activity.

United States Patent No. 5,037,825 discloses compounds having retinoid-like biological activity where a condensed heterocyclic ring such as a thiochroman is connected to a substituted phenyl ring with an ethylene, or amide (CONH) bridge. An article in Journal of American Academy of Dermatology by Sporn et. al. and an article in Journal of Medicinal Chemistry, 1988, 31, 2182-2193 (Kagechika et al.) also disclose compounds of retinoid-like biological activity where a tetrahydronaphthalene, chroman or thiochroman moiety and a benzoic acid moiety are connected by an amide (CONH) bridge.

Several co-pending applications and recently issued patents assigned to the assignee of the present application, are directed to further compounds having retinoid-like activity.

SUMMARY OF THE INVENTION

The present invention covers compounds of **Formula 1**



Formula 1

wherein the R_1 groups independently are hydrogen, lower alkyl of 1 to 6 carbons, or two geminal R_1 groups may represent an oxo (=O) or a thio (=S) group;

R_2 is hydrogen or lower alkyl of 1 to 6 carbons, or halogen;

M is $-N=CR_4-$ or $-R_4C=N-$ where R_4 is hydrogen or lower alkyl of 1 - 6 carbons;

X is $C(R_1)_2$, O, S, or NR_1;

Y is a phenyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pirimidinyl, pyrazinyl, thiazolyl, imidazolyl and oxazolyl, said phenyl group or said heteroaryl groups being optionally substituted with an R_3 group which is lower alkyl of 1 to 6 carbons or halogen;

A is $(CH_2)_n$ where n is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds, and

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$,

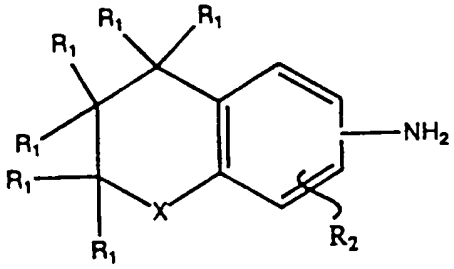
CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, or $CR_7OR_{13}O$, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons.

In a second aspect, this invention relates to the use of the compounds of **Formula 1** as regulators for cell proliferation and differentiation, and particularly as agents for treating dermatoses, such as acne, Darier's disease, psoriasis, icthyosis, eczema, atopic dermatitis, and for treating and preventing malignant hyperproliferative diseases such as epithelial cancer, breast cancer, prostatic cancer, head and neck cancer and myeloid leukemias, for reversing and preventing atherosclerosis and restenosis resulting from neointimal hyperproliferation, for treating and preventing other non-malignant hyperproliferative diseases such as endometrial hyperplasia, benign prostatic hypertrophy, proliferative vitreal retinopathy and dysplasias, for treating autoimmune diseases and immunological disorders (e.g. lupus erythematosus), for treating chronic inflammatory diseases such as pulmonary fibrosis, for treating and preventing diseases associated with lipid metabolism and transport such as dyslipidemias, for promoting wound healing, for treating dry eye syndrome and in reversing and

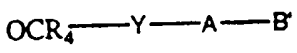
preventing the effects of sun damage to skin.

This invention also relates to a pharmaceutical formulation comprising a compound of **Formula 1** in admixture with a pharmaceutically acceptable excipient.

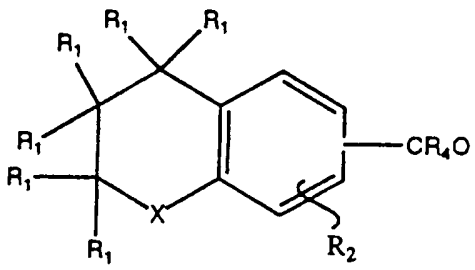
In another aspect, this invention relates to the process for making the "imine" compound of **Formula 1** which process comprises reacting in an inert solvent a primary amine of **Formula 2** with an aldehyde or ketone of **Formula 3**, or to reacting an aldehyde or ketone of **Formula 4** with a primary amine of **Formula 5**. In **Formulas 3** and **5**, **B'** is defined as **B** above, or such a protected derivative of the **B** function which does not interfere with the formation of the imine function in the indicated reactions. The remaining symbols are defined as in connection with **Formula 1**.



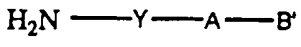
Formula 2



Formula 3



Formula 4



Formula 5

General Embodiments

Definitions

The term alkyl refers to and covers any and all groups which are known as normal alkyl, branched-chain alkyl and cycloalkyl. The term alkenyl refers to and covers normal alkenyl, branch chain alkenyl and cycloalkenyl groups having one or more sites of unsaturation. Lower alkyl means the above-defined broad definition of alkyl groups having 1 to 6 carbons, and as applicable, 3 to 6 carbons for branch chained

and cycloalkyl groups. Lower alkenyl is defined similarly having 2 to 6 carbons for normal alkenyl, and 3 to 5 carbons for branch chained and cycloalkenyl groups.

The term "ester" as used here refers to and covers any compound falling within the definition of that term as classically used in organic chemistry. It includes organic and inorganic esters. Where **B** (of **Formula 1**) is -COOH, this term covers the products derived from treatment of this function with alcohols or thioalcohols preferably with aliphatic alcohols having 1-6 carbons. Where the ester is derived from compounds where **B** is $-CH_2OH$, this term covers compounds derived from organic acids capable of forming esters including phosphorous based and sulfur based acids, or compounds of the formula $-CH_2OCOR_{11}$ where R_{11} is any substituted or unsubstituted aliphatic, aromatic, heteroaromatic or aliphatic aromatic group, preferably with 1-6 carbons in the aliphatic portions.

Preferred esters are derived from the saturated aliphatic alcohols or acids of ten or fewer carbon atoms or the cyclic or saturated aliphatic cyclic alcohols and acids of 5 to 10 carbon atoms. Particularly preferred aliphatic esters are those derived from lower alkyl acids and alcohols. Also preferred are the phenyl or lower alkyl phenyl esters.

The term "amides" has the meaning classically accorded that term in organic chemistry. In this instance it includes the unsubstituted amides and all aliphatic and aromatic mono- and di- substituted amides. Preferred amides are the mono- and di-substituted amides derived from the saturated aliphatic radicals of ten or fewer carbon atoms or the cyclic or

saturated aliphatic-cyclic radicals of 5 to 10 carbon atoms. Particularly preferred amides are those derived from substituted and unsubstituted lower alkyl amines. Also preferred are mono- and disubstituted amides derived from the substituted and unsubstituted phenyl or lower alkylphenyl amines. Unsubstituted amides are also preferred.

Acetals and ketals include the radicals of the formula-CK where K is $(-OR)_2$. Here, R is lower alkyl. Also, K may be $-OR_7O-$ where R_7 is lower alkyl of 2-5 carbon atoms, straight chain or branched.

A pharmaceutically acceptable salt may be prepared for any compound in this invention having a functionality capable of forming such-salt, for example an acid functionality. A pharmaceutically acceptable salt is any salt which retains the activity of the parent compound and does not impart any deleterious or untoward effect on the subject to which it is administered and in the context in which it is administered.

Pharmaceutically acceptable salts may be derived from organic or inorganic bases. The salt may be a mono or polyvalent ion. Of particular interest are the inorganic ions, sodium, potassium, calcium, and magnesium. Organic salts may be made with amines, particularly ammonium salts such as mono-, di- and trialkyl amines or ethanol amines. Salts may also be formed with caffeine, tromethamine and similar molecules. Where there is a nitrogen sufficiently basic as to be capable of forming acid addition salts, such may be formed with any inorganic or organic acids or alkylating agent such as methyl iodide. Preferred salts are those formed with inorganic acids such as

hydrochloric acid, sulfuric acid or phosphoric acid. Any of a number of simple organic acids such as mono-, di- or tri- acid may also be used.

Some of the compounds utilized in accordance with the present invention may have trans and cis (E and Z) isomers. In addition, the compounds of the present invention may contain one or more chiral centers and therefore may exist in enantiomeric and diastereomeric forms. The scope of the present invention is intended to cover all such isomers per se, as well as mixtures of cis and trans isomers, mixtures of diastereomers and racemic mixtures of enantiomers (optical isomers) as well.

With reference to the symbol **Y** in **Formula 1**, the preferred compounds of the invention are those where **Y** is phenyl, pyridyl, thienyl or furyl. Even more preferred are compounds where **Y** is phenyl or pyridyl. As far as substitutions on the **Y** (phenyl) and **Y** (pyridyl) groups are concerned, compounds are preferred where the phenyl group is 1,4 (para) substituted, and where the pyridine ring is 2,5 substituted. (Substitution in the 2,5 positions in the "pyridine" nomenclature corresponds to substitution in the 6-position in the "nicotinic acid" nomenclature.) The R_3 group of the aromatic or heteroaromatic ring **Y** is preferably hydrogen.

With reference to the symbol **X** in **Formula 1**, compounds are preferred in accordance with the invention where **X** is O, N-isopropyl, or $C(R_1)_2$, particularly where $C(R_1)_2$ is $C(CH_3)_2$. Generally speaking compounds are preferred where R_1 is hydrogen or methyl. The substituent R_2 in accordance with the present invention is preferably H or methyl. In the

event **X** is $C(R_1)_2$ (tetrahydronaphthalene compounds) then the R_2 substituent preferably occupies the 3-position of the 5,6,7,8-tetrahydronaphthalene nucleus. When **X** is O, S or NR_1 (chroman, thiochroman or tetrahydroquinoline derivatives) then the R_2 substituent preferably occupies the 7-position of the chroman, thiochroman or tetrahydroquinoline nucleus.

The R_4 group of the imine function (represented by **M** in **Formula 1**) of the compounds of the invention is preferably hydrogen or methyl. When **X** is $C(R_1)_2$ (tetrahydronaphthalene compounds) then the **M** substituent preferably occupies the 2-position of the 5,6,7,8-tetrahydronaphthalene nucleus. When **X** is O, S or NR_1 (chroman, thiochroman or tetrahydroquinoline derivatives) then the **M** substituent preferably occupies the 6-position of the chroman, thiochroman or tetrahydroquinoline nucleus.

Referring now to the **A - B** group of **Formula 1**, compounds are preferred in accordance with the invention where **A** is $(CH_2)_n$ where **n** is 0 to 3, and even more preferred where **n** is 0. **B** is preferably COOH (carboxylic acid or salt thereof), $COOR_8$ (ester), or $CONR_9R_{10}$ (amide).

The most preferred compounds of the invention are listed in **Table 1** with reference to **Formulas 6** and **7**.

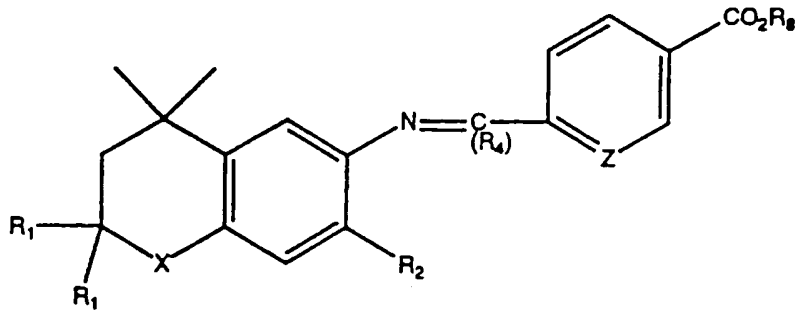
Table 1

Compounds of Formula 6

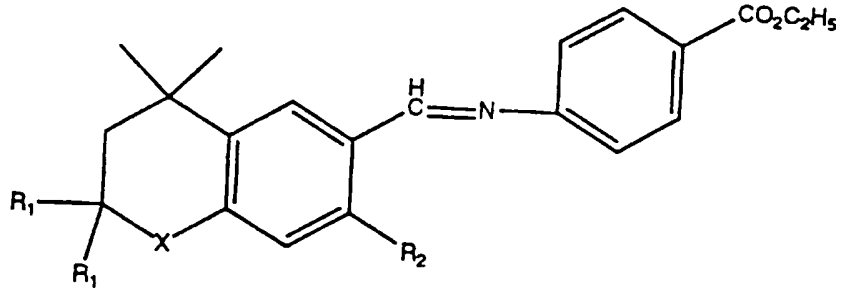
Compound #	R_1,R_1	X	R_2	R_4	Z	R_8
1	H,H	$C(CH_3)_2$	H	H	CH	CH_3
2	H,H	$C(CH_3)_2$	H	H	CH	H
3	H,H	$C(CH_3)_2$	CH_3	H	CH	H
4	H,H	$C(CH_3)_2$	H	H	CH	C_2H_5
5	H,H	$C(CH_3)_2$	H	CH_3	CH	C_2H_5
6	H,H	$C(CH_3)_2$	CH_3	H	CH	C_2H_5
7	H,H	$C(CH_3)_2$	H	H	N	C_2H_5
8	O	N-i-propyl	H	H	CH	C_2H_5

Compounds of Formula 7

Compound #	R_1,R_1	X	R_2
9	H,H	$C(CH_3)_2$	H
10	CH_3,CH_3	O	H
11	H,H	$C(CH_3)_2$	CH_3



Formula 6



Formula 7

The compounds of this invention may be administered systemically or topically, depending on such considerations as the condition to be treated, need for site-specific treatment, quantity of drug to be administered, and numerous other considerations.

In the treatment of dermatoses, it will generally be preferred to administer the drug topically, though in certain cases such as treatment of severe cystic acne or psoriasis, oral administration may also be used. Any common topical formulation such as a solution, suspension, gel, ointment, or salve and the like may be used. Preparation of such topical formulations are well described in the art of pharmaceutical formulations as exemplified, for example, Remington's Pharmaceutical Science, Edition 17, Mack Publishing Company, Easton, Pennsylvania. For topical application, these compounds could also be administered as a powder or spray, particularly in

aerosol form. If the drug is to be administered systemically, it may be confected as a powder, pill, tablet or the like or as a syrup or elixir suitable for oral administration. For intravenous or intraperitoneal administration, the compound will be prepared as a solution or suspension capable of being administered by injection. In certain cases, it may be useful to formulate these compounds by injection. In certain cases, it may be useful to formulate these compounds in suppository form or as extended release formulation for deposit under the skin or intramuscular injection.

Other medicaments can be added to such topical formulation for such secondary purposes as treating skin dryness; providing protection against light; other medications for treating dermatoses; medicaments for preventing infection, reducing irritation, inflammation and the like.

Treatment of dermatoses or any other indications known or discovered to be susceptible to treatment by retinoic acid-like compounds will be effected by administration of the therapeutically effective dose of one or more compounds of the instant invention. A therapeutic concentration will be that concentration which effects reduction of the particular condition, or retards it expansion. In certain instances, the compound potentially may be used in prophylactic manner to prevent onset of a particular condition.

A useful therapeutic or prophylactic concentration will vary from condition to condition and in certain instances may vary with the severity of the condition being treated and the patient's susceptibility to treatment. Accordingly, no single concentration will

be uniformly useful, but will require modification depending on the particularities of the disease being treated. Such concentrations can be arrived at through routine experimentation. However, it is anticipated that in the treatment of, for example, acne, or similar dermatoses, that a formulation containing between 0.01 and 1.0 milligrams per mililiter of formulation will constitute a therapeutically effective concentration for total application. If administered systemically, an amount between 0.01 and 5 mg per kg per day of body weight would be expected to effect a therapeutic result in the treatment of many disease for which these compounds are useful.

The retinoic acid-like activity of these compounds is confirmed through the classic measure of retinoic acid activity involving the effects of retinoic acid on ornithine decarboxylase. The original work on the correlation between retinoic acid and decrease in cell proliferation was done by Verma & Boutwell, Cancer Research, 1977, 37,2196-2201. That reference discloses that ornithine decarboxylase (ODC) activity increased precedent to polyamine biosynthesis. It has been established elsewhere that increases in polyamine synthesis can be correlated or associated with cellular proliferation. Thus, if ODC activity could be inhibited, cell hyperproliferation could be modulated. Although all cases for ODC activity increases are unknown, it is known that 12-0-tetradecanoylphorbol-13-acetate (TPA) induces ODC activity. Retinoic acid inhibits this induction of ODC activity by TPA. An assay essentially following the procedure set out in Cancer Research: 1662-1670,1975 may be used to demonstrate inhibition of TPA induction of ODC by

compounds of this invention. Activity of exemplary compounds of the present invention in the above-described ODC assay is disclosed in **Table 2** which provides the IC_{80} concentration for the respective exemplary compound. ("IC_{80}" is that concentration of the test compound which causes 80% inhibition in the ODC assay)

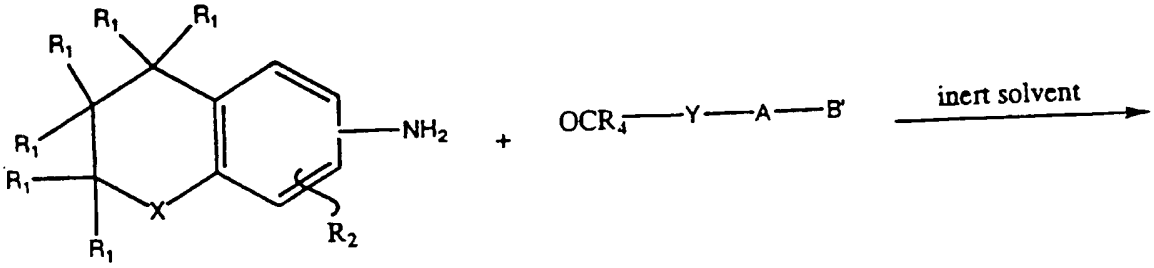
TABLE 2

Compound#	IC_{80} conc (nmols)
1	14.5
4	2.5
5	5.5
6	293
7	>30
9	9.6
10	44.0
11	3.5

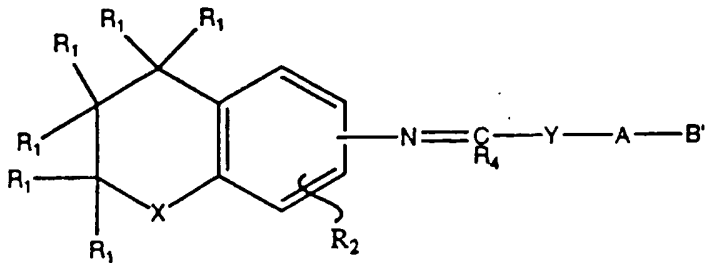
Specific Embodiments

The compounds of this invention can be made by the synthetic chemical pathways illustrated here. The synthetic chemist will readily appreciate that the conditions set out here are specific embodiments which can be generalized to any and all of the compounds represented by **Formula 1**. Generally speaking, the compounds of the present invention are imines of unique chemical structure, which are synthesized by the reaction of an aldehyde or ketone with a primary amine. **Reaction Scheme 1** illustrates in general terms synthesis of those compounds of the present invention which are derived from a primary amine of **Formula 2**, and **Reaction Scheme 2** illustrates synthesis of those compounds of the invention which are derived from a ketone or aldehyde of **Formula 4**. In other words,

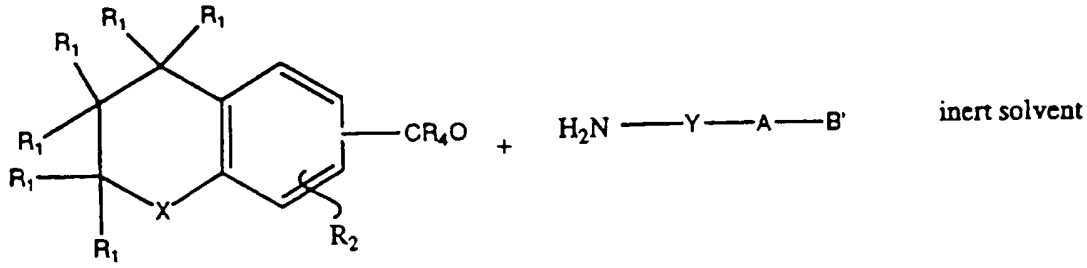
Reaction Scheme 1 illustrates synthesis of those compounds of **Formula 1** where the symbol **M** represents $-N=CR_4-$. These compounds are represented by **Formula 8** in the reaction scheme. **Reaction Scheme 2** illustrates synthesis of those compounds of **Formula 1** where the symbol **M** represents $-R_4C=N-$. The latter compounds are represented by **Formula 9** in the reaction scheme. The reactions illustrated in these schemes are usuallly conducted in an anhydrous inert solvent, such as dichloromethane, benzene, or tetrahydrofuran, at room temperature or under reflux conditions, in the presence of a drying agent, such as molecular sieves or anhydrous magnesium sulfate. The imine product of the reaction can typically be obtained by evaporation of the solvent, followed by crystallization or chromatography.



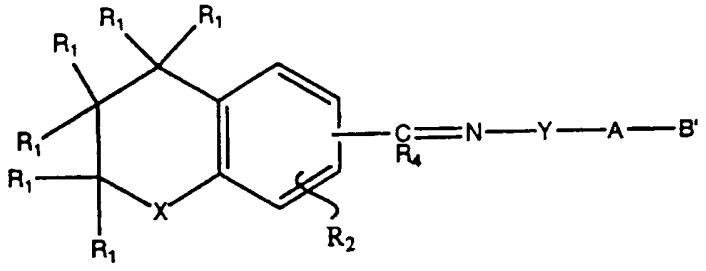
Formula 2 Formula 3



Formula 8 **Reaction Scheme 1**



Formula 4 Formula 5



Formula 9

Reaction Scheme 2

Generally speaking the starting material primary amines and aldehydes or ketones, that is the respective compounds of **Formula 2**, **5**, **3** and **4** are available commercially or can be obtained in accordance with procedures described in the chemical literature. For example, 2-amino-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene (2-aminotetramethyltetralin, **Compound 20**) can be obtained in accordance with the procedure described in the article Journal of Medicinal Chemistry, 1988, 31, 2182-2193 (Kagechika et al.) which is incorporated herein by reference. This reagent (**Compound 20**) is used for the synthesis of exemplary

Compounds 1, 2, 4, 5 and **7**. The corresponding 3-methyl compound (2-amino-5,6,7,8-tetrahydro-3,5,5,8,8-pentamethylnaphthalene **Compound 21**) can also be obtained in accordance with the Kagechika et al. reference. This compound is utilized in the synthesis of exemplary compounds **3** and **6** of the present invention.

5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthalene-2-carboxaldehyde (**Compound 22**) is used as starting material for the synthesis of exemplary **Compound 9** of the present invention. **Compound 22** can be obtained in accordance with the procedure of Journal of Medicinal Chemistry, 1989, 32, p1098 (Kagechika et al. II), incorporated herein by reference. 5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethylnaphthalene-2-carboxaldehyde (**Compound 23**) is used for the synthesis of exemplary **Compound 11** of the present invention. **Compound 23** can be obtained in accordance with United States Patent No. 4,950,369, the specification of which is incorporated herein by reference.

2,2,4,4-tetramethyl-6-chromanaldehyde (**Compound 24**) is used in the condensation reaction which produces exemplary **Compound 10** of the present invention. **Compound 24** is obtained by reduction of 2,2,4,4-tetramethyl-chroman-6-carboxylic acid and subsequent oxidation of the resulting primary alcohol. 2,2,4,4-tetramethyl-6-chromanaldehyde (**Compound 24**)is described in United States Patent No. 5,006,550, the specification of which is incorporated here by reference.

Methyl 4-formylbenzoate (**Compound 25**), 4-carboxybenzaldehyde (**Compound 26**) 4-carboxyacetophenone (**Compound 27**) and ethyl 4-formylbenzoate (**Compound 28**)

are reagents corresponding to **Formula 3** in accordance with **Reaction Scheme 1**, and are used for the synthesis of exemplary **Compounds 1 - 6** and **8** of the present invention. **Compounds 25, 26** and **27** are available from Aldrich Chemical Co., and **Compound 28** can be obtained in accordance with Journal of Medicinal Chemistry 1981, 24, p583 (Dawson et al.) incorporated herein by reference.

Ethyl 4-aminobenzoate (**Compound 29**) is a commercially available reagent (Aldrich) which is represented by **Formula 5** in **Reaction Scheme 2** and is used for preparing exemplary **Compounds 9 - 11** of the present invention.

Further examples of compounds represented by **Formula 2** which can be used in the condensation reactions with compounds of **Formula 3** to provide additional compounds of the invention are as follows:

2-amino-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethylnaphthalene;

2-amino-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-propylnaphthalene;

2-amino-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-chloronaphthalene;

2-amino-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-bromonaphthalene;

3-amino-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene;

3-amino-5,6,7,8-tetrahydro-2,5,5,8,8-pentamethylnaphthalene;

3-amino-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-ethylnaphthalene;

3-amino-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-propylnaphthalene;

3-amino-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-chloronaphthalene;

3-amino-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-bromonaphthalene;

6-amino-4,4-dimethylchroman;

6-amino-4,4,7-trimethylchroman;

6-amino-2,2,4,4-tetramethylchroman;

6-amino-2,2,4,4,7-pentamethylchroman;

7-amino-4,4-dimethylchroman;

7-amino-4,4,6-trimethylchroman;

7-amino-2,2,4,4-tetramethylchroman;

7-amino-2,2,4,4,6-pentamethylchroman;

6-amino-4,4-dimethylthiochroman;

6-amino-4,4,7-trimethylthiochroman;

6-amino-2,2,4,4-tetramethylthiochroman;

6-amino-2,2,4,4,7-pentamethylthiochroman;

7-amino-4,4-dimethylthiochroman;

7-amino-4,4,6-trimethylthiochroman;

7-amino-2,2,4,4-tetramethylthiochroman;

7-amino-2,2,4,4,6-pentamethylthiochroman;

6-amino-4,4-dimethyl-1,2,3,4-tetrahydroquinoline;

6-amino-4,4,7-trimethyl-1,2,3,4-tetrahydroquinoline;

6-amino-2,2,4,4-tetramethyl-1,2,3,4-tetrahydroquinoline;

6-amino-2,2,4,4,7-pentamethyl-1,2,3,4-tetrahydroquinoline;

7-amino-4,4-dimethyl-1,2,3,4-tetrahydroquinoline;

7-amino-4,4,6-trimethyl-1,2,3,4-tetrahydroquinoline;

7-amino-2,2,4,4-tetramethyl-1,2,3,4-tetrahydroquinoline;

7-amino-2,2,4,4,6-pentamethyl-1,2,3,4-

tetrahydroquinoline;

Further examples of compounds of **Formula 3** are:

methyl 6-carboxynicotinate;

nicotinic acid 6-carboxaldehyde;

3-carboxy-thiophene-5-carboxaldehyde;

3-methoxycarbonyl-thiophene-5-carboxaldehyde;

3-ethoxycarbonyl-thiophene-5-carboxaldehyde;

2-carboxy-thiophene-5-carboxaldehyde;

2-methoxycarbonyl-thiophene-5-carboxaldehyde;

2-ethoxycarbonyl-thiophene-5-carboxaldehyde;

3-carboxy-furan-5-carboxaldehyde;

3-methoxycarbonyl-furan-5-carboxaldehyde;

3-ethoxycarbonyl-furan-5-carboxaldehyde;

2-carboxy-furan-5-carboxaldehyde;

2-methoxycarbonyl-furan-5-carboxaldehyde;

2-ethoxycarbonyl-furan-5-carboxaldehyde;

Still further, additional examples of compounds represented by **Formula 4** which can be used in the condensation reactions with compounds of **Formula 5** to provide additional compounds of the invention are as follows:

5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethylnaphthalene-2-carboxaldehyde;

5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-propylnaphthalene-
-2-carboxaldehyde;

5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-chloronaphthalene-
-2-carboxaldehyde;

5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-bromonaphthalene-2-carboxaldehyde;

5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-3-carboxaldehyde;

5,6,7,8-tetrahydro-2,5,5,8,8-pentamethylnaphthalene-3-carboxaldehyde;

5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-ethylnaphthalene-3-carboxaldehyde;

5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-propylnaphthalene-3-carboxaldehyde;

5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-chloronaphthalene-3-carboxaldehyde;

5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-bromonaphthalene-3-carboxaldehyde;

4,4-dimethylchroman-6-carboxaldehyde;

4,4,7-trimethylchroman-6-carboxaldehyde;

2,2,4,4,7-pentamethylchroman-6-carboxaldehyde;

4,4-dimethylchroman-7-carboxaldehyde;

4,4,6-trimethylchroman-7-carboxaldehyde;

2,2,4,4-tetramethylchroman-7-carboxaldehyde;

2,2,4,4,6-pentamethylchroman-7-carboxaldehyde;

4,4-dimethylthiochroman-6-carboxaldehyde;

4,4,7-trimethylthiochroman-6-carboxaldehyde;

2,2,4,4-tetramethylthiochroman-6-carboxaldehyde;

2,2,4,4,7-pentamethylthiochroman-6-carboxaldehyde;

4,4-dimethylthiochroman-7-carboxaldehyde;

4,4,6-trimethylthiochroman-7-carboxaldehyde;

2,2,4,4-tetramethylthiochroman-7-carboxaldehyde;

2,2,4,4,6-pentamethylthiochroman-7-carboxaldehyde;

4,4-dimethyl-1,2,3,4-tetrahydroquinoline-6-carboxaldehyde;

4,4,7-trimethyl-1,2,3,4-tetrahydroquinoline-6-carboxaldehyde;

2,2,4,4-tetramethyl-1,2,3,4-tetrahydroquinoline-6-carboxaldehyde;

2,2,4,4,7-pentamethylmethyl-1,2,3,4-tetrahydroquinoline-6-carboxaldehyde;

4,4-dimethyl-1,2,3,4-tetrahydroquinoline-7-carboxaldehyde;

4,4,6-trimethyl-1,2,3,4-tetrahydroquinoline-7-carboxaldehyde;

2,2,4,4-tetramethyl-1,2,3,4-tetrahydroquinoline-7-carboxaldehyde;

2,2,4,4,6-pentamethyl-1,2,3,4-tetrahydroquinoline-7-carboxaldehyde;

Compounds of **Formula 5**:

methyl 6-aminonicotinate;

6-amino-nicotinic acid;

2-amino-thiophene-4-carboxylic acid;

methyl 2-amino-thiophene-4-carboxylate;

ethyl 2-amino-thiophene-4-carboxylate;

2-amino-thiophene-5-carboxylic acid;

methyl 2-amino-thiophene-5-carboxylate;

ethyl 2-amino-thiophene-5-carboxylate;

2-amino-furan-4-carboxylic acid;

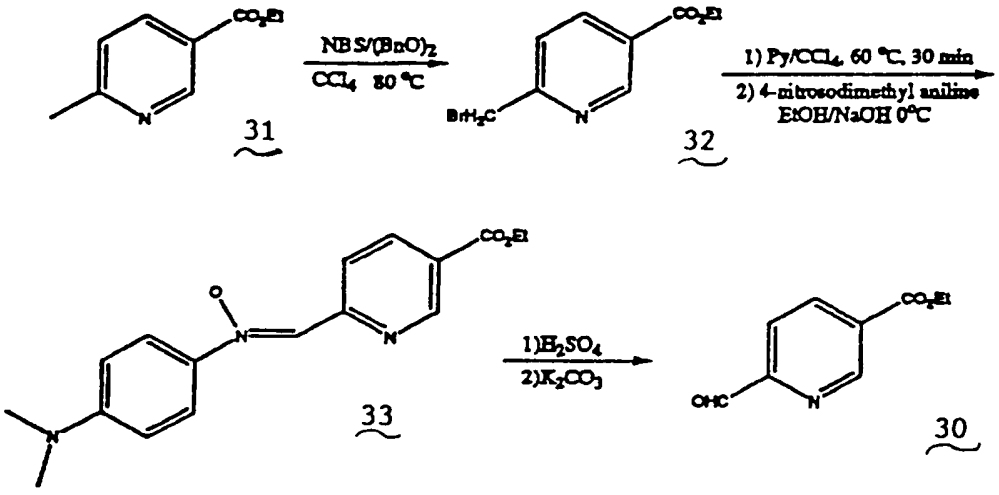
methyl 2-amino-furan-4-carboxylate;

ethyl 2-amino-furan-4-carboxylate;

2-amino-furan-5-carboxylic acid;

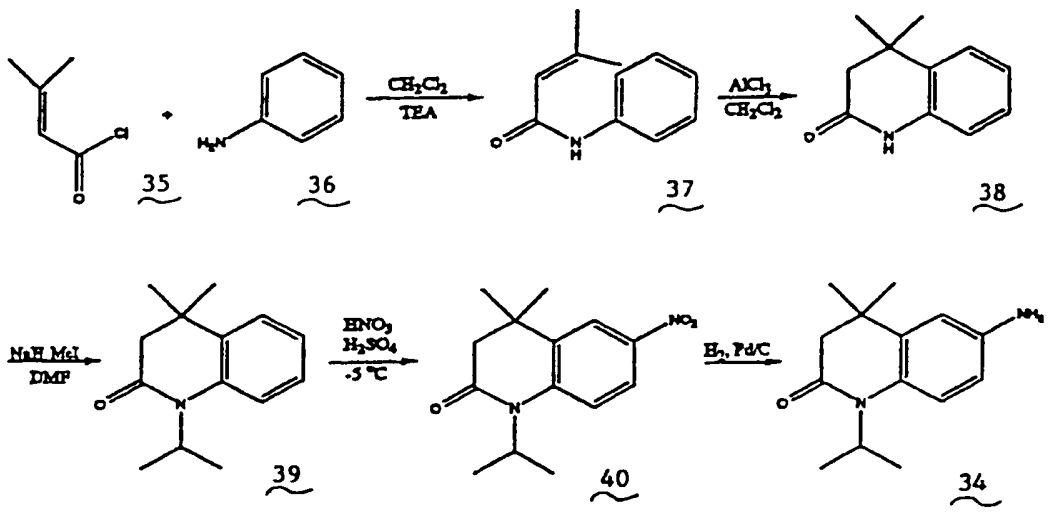
methyl 2-amino-furan-5-carboxylate;

ethyl 2-amino-furan-5-carboxylate.



Reaction Scheme 3

The reagent ethyl 6-carboxynicotinate (**Compound 30**) is used for the synthesis of exemplary **Compound 7** of the present invention. **Compound 30** is obtained in accordance with **Reaction Scheme 3**, wherein ethyl 6-methylnicotinate (**Compound 31**, available from Aldrich) is reacted with N-bromosuccinimide and benzoylperoxide to yield ethyl 6-bromomethylnicotinate (**Compound 32**). The latter compound is reacted with pyridine and subsequently with N,N-dimethyl-4-nitrosoaniline and base to provide 4-ethoxycarbonyl-6-pyridylaldehyde N-(4-dimethylamino)phenyl oxime (**Compound 33**), which is subsequently hydrolyzed to yield ethyl 6-carboxynicotinate (**Compound 30**).



Reaction Scheme 4

Reaction Scheme 4 illustrates the synthesis of N-isopropyl 4,4-dimethyl-2-oxo-6-aminoquinoline (**Compound 34**), which is used in accordance with **Reaction Scheme 1** to synthesize exemplary **Compound 8** of the present invention. Thus, 3,3-dimethylacryloyl chloride (**Compound 35**, available from Aldrich) is reacted with aniline (**Compound 36**) to yield N-3,3-dimethylacryloyl aniline (**Compound 37**). **Compound 37** is ring closed under Friedel Crafts conditions to yield 4,4-dimethyl-2-oxoquinoline (**Compound 38**) which is thereafter alkylated with iso-propyl iodide to give N-isopropyl 4,4-dimethyl-2-oxoquinoline (**Compound 39**). Nitration of **Compound 39** yields N-isopropyl 4,4-

dimethyl-2-oxo-6-nitroquinoline **Compound 40**, which is reduced with hydrogen on palladium to give **Compound 34**.

As it is apparent from the foregoing, the reagents of **Formulas 2 - 5** which give rise to the compounds of the present invention are either known compounds, or can be synthesized in synthetic routes generally within the skill of the art. Compounds of the invention in accordance with **Formula 1** can also be subjected to certain synthetic conversions or transformations, which produce still further compounds of the invention. Alternatively, blocked or protected derivatives of the compounds of the invention may be obtained in accordance with **Reaction Schemes 1** and **2**, and such blocked or protected derivatives can be converted into compounds of the invention in chemical reactions well known in the art. Such known chemical reactions can also be routinely utilized for the synthesis of the reagents of **Formulas 2 - 5**. In connection with the foregoing the following well known and published synthetic methodology is noted.

Carboxylic acids are typically esterified by refluxing the acid in a solution of the appropriate alcohol in the presence of an acid catalyst such as hydrogen chloride or thionyl chloride. Alternatively, the carboxylic acid can be condensed with the appropriate alcohol in the presence of dicyclohexylcarbodiimide and dimethylaminopyridine. The ester is recovered and purified by conventional means. Acetals and ketals are readily made by the method described in March, "Advanced Organic Chemistry," 2nd Edition, McGraw-Hill Book Company, p 810). Alcohols, aldehydes and ketones all may be protected by forming respectively, ethers and esters,

acetals or ketals by known methods such as those described in McOmie, Plenum Publishing Press, 1973 and Protecting Groups, Ed. Greene, John Wiley & Sons, 1981.

To increase the value of **n** in the compounds of **Formula 3** and **5** before affecting the condensation reaction of **Reaction Schemes 1** and **2** (where such compounds corresponding to **Formula 3** and **5** are not available from a commercial source) aromatic or heteroaromatic carboxylic acids are subjected to homologation by successive treatment under Arndt-Eistert conditions or other homologation procedures. Alternatively, derivatives which are not carboxylic acids may also be homologated by appropriate procedures. The homologated acids can then be esterified by the general procedure outlined in the preceding paragraph.

Compounds of **Formula 3**, or of **Formula 5** where **A** is an alkenyl group having one or more double bonds can be made for example, by synthetic schemes well known to the practicing organic chemist; for example by Wittig and like reactions, or by introduction of a double bond by elimination of halogen from an alpha-halo-arylalkyl-carboxylic acid, ester or like carboxaldehyde. Compounds of **Formula 3** or of **Formula 5** where the **A** group has a triple (acetylenic) bond can be made by reaction of a corresponding aromatic-methyl ketone with strong base, such as lithium diisopropyl amide.

The acids and salts derived from compounds of **Formula 3** or of **Formula 5** or in appropriate cases of **Formula 1**, are readily obtainable from the corresponding esters. Basic saponification with an alkali metal base will provide the acid. For example, an ester may be dissolved in a polar solvent such as an

alkanol, preferably under an inert atmosphere at room temperature, with about a three molar excess of base, for example, lithium hydroxide or potassium hydroxide. The solution is stirred for an extended period of time, between 15 and 20 hours, cooled, acidified and the hydrolysate recovered by conventional means.

The amide may be formed by any appropriate amidation means known in the art from the corresponding esters or carboxylic acids. One way to prepare such compounds is to convert an acid to an acid chloride and then treat that compound with ammonium hydroxide or an appropriate amine. For example, the acid is treated with an alcoholic base solution such as ethanolic KOH (in approximately a 10% molar excess) at room temperature for about 30 minutes. The solvent is removed and the residue taken up in an organic solvent such as diethyl ether, treated with a dialkyl formamide and then a 10-fold excess of oxalyl chloride. This is all effected at a moderately reduced temperature between about -10 degrees and +10 degrees C. The last mentioned solution is then stirred at the reduced temperature for 1-4 hours, preferably 2 hours. Solvent removal provides a residue which is taken up in an inert organic solvent such as benzene, cooled to about 0 degrees C and treated with concentrated ammonium hydroxide. The resulting mixture is stirred at a reduced temperature for 1 - 4 hours. The product is recovered by conventional means.

Alcohols are made by converting the corresponding acids to the acid chloride with thionyl chloride or other means (J. March, "Advanced Organic Chemistry", 2nd Edition, McGraw-Hill Book Company), then reducing the acid chloride with sodium borohydride (March, Ibid,

pg. 1124), which gives the corresponding alcohols. Alternatively, esters may be reduced with lithium aluminum hydride at reduced temperatures. Alkylating these alcohols with appropriate alky halides under Williamson reaction conditions (March, Ibid, pg. 357) gives the corresponding ethers. These alcohols can be converted to esters by reacting them with appropriate acids in the presence of acid catalysts or dicyclohexylcarbodiimide and dimethlaminopyridine.

Aldehydes can be prepared from the corresponding primary alcohols using mild oxidizing agents such as pyridinium dichromate in methylene chloride (Corey, E. J., Schmidt, G., Tet. Lett., 399, 1979), or dimethyl sulfoxide/oxalyl chloride in methylene chloride (Omura, K., Swern, D., Tetrahedron, 1978, 34, 1651).

Ketones can be prepared from an appropriate aldehyde by treating the aldehyde with an alkyl Grignard reagent or similar reagent followed by oxidation.

Acetals or ketals can be prepared from the corresponding aldehyde or ketone by the method described in March, Ibid, p 810.

Compounds of **Formula 3** or of **Formula 5** where **B** is H can be prepared from the corresponding halogenated aromatic or hetero aromatic compounds, preferably where the halogen is I.

The following specific examples further illustrate the invention and describe the best mode thereof.

Specific Examples

N-3,3-Dimethylacryloyl Aniline **(Compound 37)**

In a 100 mL round bottom flask was placed NaH (1.93 g, 0.05 mol). After washing with dry hexane (2x10 mL dry THF (15 mL) was added), to this tan solid.

Then, the resulting suspension was added to a solution of aniline (**Compound 36**, 4.89 mL, 0.054 mol) in dry THF (7 mL) at 0 ^{o} C. After stirring for 30 min, 3,3-dimethylacryloyl chloride (**Compound 35**, 6.56 mL, 0.059 mol) was added dropwise to the above solution. The reaction mixture was stirred under N_2 for overnight followed by a slow addition of water. The mixture was extracted with ethyl acetate (2x20 mL). The combined organic layers were washed with NH_4Cl (sat.) and NaCl (sat.), dried over $MgSO_4$ and concentrated to give the title compound as a tan solid (4.45 g, 51%). ^{1}H NMR d 1.87 (s, 3H), 2.21 (s, 3H), 5.72 (s, 1H), 7.29-7.56 (m, 5H).

4,4-Dimethyl-2-oxoquinoline (**Compound 38**)

To a 500 mL round bottom flask containing $AlCl_3$ (5.22g, 0.039 mol) was added dry CH_2Cl_2 (40 mL). Then a solution of N-(3,3-dimethylacryloyl) aniline (**Compound 37**, 4.45 g, 0.025 mol) in CH_2Cl_2 (50 mL) was added slowly. The reaction mixture was stirred at room temperature for overnight followed by the addition of ice-cubes. This mixture was extracted with ethyl acetate (2x20 mL). The combined organic layers were washed with NaCl (sat.), dried over $MgSO_4$ and concentrated to give a brownish oil. Purification of this oil by column chromatography (10% ethyl acetate in hexane) gave the title compound as a light yellow solid (2.31 g, 52%). ^{1}H NMR d 1.34 (s, 6H), 2.51 (s, 2H), 6.85 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.03-7.08 (m, 1H), 7.16-7.23 (m, 1H), 9.01 (b, 1H).

N-Isopropyl 4,4-dimethyl-2-oxoquinoline (**Compound 39**)

To a suspension of NaH (0.121 g, 3.0 mmol) in dry DMF (2 mL) was added a solution of 4,4,-dimethyl-2-oxo-quinoline (**Compound 38**, 0.529 g, 3.0 mmol) in dry DMF

(10 mL). The mixture was stirred at room temperature for 30 min followed by addition of isopropyl iodide. The reaction mixture was left at room temperature for 72 h. Then ice-cubes were added to the reaction and the mixture was extracted with ethyl acetate (2x5 mL). The combined organic layers were washed with saturated solution of NaCl, dried over $MgSO_4$ and concentrated to give a pale yellow oil. Purification by column chromatography (silica gel, 30% ethyl acetate in hexane) yielded the title compound as a colorless oil (472 mg, 72%). ^1H NMR d 1.32 (s, 6H), 1.57 (d, J = 7.1 Hz, 6H), 2.45 (s, 2H), 4.74 (q, J = 7.0 Hz, 1H), 7.06-7.32 (m, 4H).

N-Isopropyl 4,4-dimethyl-2-oxo-6-nitroquinoline (**Compound 40**)

N-Isopropyl 4,4,-dimethyl-2-oxo-quinoline (**Compound 39**, 472 mg, 2.18 mmol) was added dropwise to H_2SO_4 (con. 0.3 mL) cooled to -5 ^{o} C with a salt-ice bath. To this brown oil was added a mixture of HNO_3 (0.16 mL) and H_2SO_4 (0.65 mL) at a rate so slow that the internal temperature did not exceed 0 ^{o} C. The resulting dark oil was stirred vigorously for 10 minutes, followed by addition of ice-water. The yellow reaction mixture was extracted with ethyl acetate (2x5 mL). The combined organic layers were washed with $NaHCO_3$ (10%), dried over $MgSO_4$ and concentrated to give yellow solids. ^1H NMR d 1.34 (s, 6H), 1.53(d, J = 6.8 Hz, 6H), 2.48 (s, 2H), 4.70-4.79 (m, 1H), 7.25 (d, J = 6.3 Hz, 1H), 8.10-8.15 (m, 2H).

N-Isopropyl 4,4-dimethyl-2-oxo-6-aminoquinoline (**Compound 34**)

N-Isopropyl 4,4,-dimethyl-2-oxo-6-nitroquinoline (**Compound 40**, 220 mg, 0.84 mmol) was dissolved in CH_3OH

(3 ml). The solution was cleansed by flushing with N_2 gas, and thereafter a catalytic amount of 10% Pd/C was added. The resulting mixture was hydrogenated at room temperature for 5 hours. After evaporation of the solvent the title compound was obtained in quantitative yield as a light purple oil. (184.2 mg 94%) ^{1}H NMR d 1.23 (s, 6H), 1.49 (d, J = 7.0 Hz, 6H), 2.36 (s, 2H), 4.68 (q, J = 7.0 Hz, 1H), 6.55 (dd, J_1 = 2.8 Hz, J_2 = 8.6 Hz, 1H), 6.64 (d, J = 2.6 Hz, 1H), 6.94 (d, J = 8.6 Hz, 1H).

Ethyl 6-bromomethyl nicotinate (**Compound 32**)

A mixture of ethyl 6-methylnicotinate (**Compound 31**, 0.473 g, 2.87 mmol), N-bromosuccinimide (561 mg, 3.15 mmol) and benzoyl peroxide (0.007 g, 0.03 mmol) in CCl_4 (20 mL) was refluxed for overnight. The reaction mixture was concentrated and the residue was purified by column chromatography with 20% ethyl acetate in hexane to yield the title compound as a colorless oil (0.65 g, 93%). ^{1}H NMR d 1.42 (t, J = 7.1 Hz, 3H), 4.43 (q, J = 7.1 Hz, 2H), 4.59 (s, 2H), 7.52 (d, J = 8.3 Hz, 1H), 8.29 (dd, J_1 = 2.1 Hz, J_2 = 8.7 Hz, 1H), 9.18 (d, J = 2.1 Hz, 1H).

4-Ethoxycarbonyl-6-pyridylaldehyde N-(4-dimethylamino)phenyl oxime (**Compound 33**)

A mixture of ethyl 6-bromomethyl nicotinate (**Compound 32**, 0.65 g, 2.65 mmol) and pyridine (0.23 g, 2.91 mmol) in CCl_4 (5 mL) was heated at 70 ^{o} C for 30 min. The solvent was evaporated and the residual dark-red oil was dissolved in EtOH (20 mL). To this dark colored solution was added a solution of N,N-dimethyl-4-nitroso aniline (0.438 g, 2.91 mmol) in EtOH (5 mL). This solution was chilled to 0 ^{o} C and an aqueous solution of NaOH (1N, 2.7 mL) was added

dropwise. After stirring at 0 °C for 1 hour, the reaction mixture was concentrated. The residue was dissolved in water and extracted with ethyl acetate. The organic layer was dried, concentrated and the resulting red oil was purified by column chromatography (silica gel, 30% ethyl acetate in hexane) to give the title compound as a red solid. ^{1}H NMR d 1.45 (t, J = 7.1 Hz, 3H), 4.46 (q, J = 7.1 Hz, 2H), 3.06 (s, 6H), 6.71 (d, J = 9.3 Hz, 2H), 7.75 (d, J = 9.3 Hz, 2H), 8.32 (s, 1H), 8.41 (dd, J_1 = 2.1 Hz, J_2 = 8.6 Hz, 1H), 9.24 (d, J = 2.1 Hz, 1H), 9.38 (d, J = 8.7 Hz, 1H).

Ethyl 6-Carboxynicotinate (**Compound 30**)

4-Ethoxycarbonyl-6-pyridylaldehyde N-(4-dimethylamino)phenyl oxime (**Compound 33**, 110 mg, 0.35 mmol) was added slowly to a chilled mixture of H_2SO_4 (1N, 10 mL) and ethyl ether (10 mL). The mixture was stirred at 0 °C for 1 hour followed by addition of an aqueous solution of NaOH until the pH of the aqueous phase reached 8. The mixture was extracted with ethyl acetate (3x10 mL), and the combined organic extracts were dried and concentrated to give the title compound as a yellow solid. (51 mg, 81%) ^{1} H NMR d 1.44 (t, J = 7.1 Hz, 3H), 4.44 (q, J = 7.1 Hz, 2H), 8.27 (d, J = 8.2 Hz, 1H), 8.36 (d, J = 8.3 Hz, 1H), 8.72 (s, 1H), 9.25 (s, 1H).

2,2,4,4-Tetramethyl-6-chroman aldehyde (**Compound 24**)

To a solution of 2,2,4,4-tetramethylchroman 6-carboxylic acid (0.28 g, 1.2 mmol) in THF (5 ml) under N_2 was added 1 M of $LiALH_4$/THF (1.15 ml, 1.15 mmol). The reaction mixture was left at room temperature for overnight, followed by addition of ice-water to the reaction. The reaction mixture was extracted with ethyl acetate, the organic extracts were dried and

concentrated to give 2,2,4,4-tetramethyl-chroman-6-yl methanol as a white solid. Without further purification, the alcohol was dissolved in CH_2Cl_2 (5 ml) and MnO_2 (1.04 g, 12 mmol) was added. The resulting mixture was stirred at room temperature for 5 hours. After filtration, the resulting colorless clear solution was concentrated and purified by column chromatography (silica gel, 10% ethyl acetate in hexane) to give the title compound as a colorless oil (0.147 g, 57%). ^1H NMR d 1.39 (d, 12H), 1.88 (s, 2H), 6.89 (d, J = 8.4 Hz, 1H), 7.62 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 7.85 (d, J = 2.0 Hz, 1H), 9.86 (s, 1H).

N-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-)naphthalenyl 4-methoxycarbonyl benzaldimine (**Compound 1**)

To a solution of 2-amino-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene (**Compound 20**, 0.086 g, 0.42 mmol) in dry dichloromethane (5 mL) was added 4-methoxycarbonyl benzaldehyde (**Compound 25**, 0.075 g, 0.42 mmol). The reaction mixture was stirred at room temperature for 30 min and then concentrated under vacuum to yield a yellow oil. Purification of the desired imine by flash column chromatography (silica gel, 20% ethyl acetate in hexane) yielded yellow solids (0.143 g, 97%) which were recrystallized from CH_2Cl_2/hexane to give the title compound as yellow crystals (107 mg, 69%). ^1H NMR d 1.32 (d, J = 8.0 Hz, 12H), 1.71 (s, 4H), 3.95 (s, 3H), 7.03 (dd, J_1 = 2.1 Hz, J_2 = 8.3 Hz, 1H), 7.22 (d, J = 2.3 Hz, 1H), 7.35 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H), 8.14 (d, J = 8.3 Hz, 2H), 8.54 (s, 1H).

N-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl)-2-naphthalenyl 4-carboxy benzaldimine (**Compound 2**)

A solution of 2-amino-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene (**Compound 20**, 0.106 g, 0.52 mmol) together with 4-carboxybenzaldehyde (**Compound 26**, 0.071 g, 0.47 mmol) in THF (5.0 ml) was stirred at room temperature in the presence of $MgSO_4$ for 2 days. The reaction mixture was filtered through celite and the clear yellow solution was concentrated under reduced pressure to give yellow solids. The solids were successively washed with hexane until no tetramethyltetralin amine presented in the hexane layer (checked by TLC). The title compound was obtained as a light yellow solid (0.093 g, 60%). ^1H NMR d 1.32 (d, 12H), 1.72 (s, 4H), 7.06 (dd, J_1 = 2.2 Hz, J_2 = 8.4 Hz, 1H), 7.24 (d, J = 2.2 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 8.01 (d, J = 8.4 Hz, 2H), 8.21 (d, J = 8.4 Hz, 2H), 8.56 (s, 1H).

<u>N-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl)-2-naphthalenyl 4-carboxy benzaldimine</u> (**Compound 3**)

A solution of 2-amino-5,6,7,8-tetrahydro-3,5,5,8,8-pentamethylnaphthalene 2-aminopentamethyltetralin, (**Compound 21**, 0.088 g, 0.41 mmol) together with 4-carboxybenzaldehyde (**Compound 26**, 0.052 g, 0.34 mmol) in THF (5.0 ml) was stirred at room temperature in the presence of $MgSO_4$ for 2 days. The reaction mixture was filtered through celite and the clear yellow solution was concentrated under reduced pressure to give yellow solids. The yellow solids were washed with hexane until no 2-aminopentamethyltetralin appeared in the hexane layer (checked by TLC). The title compound was obtained as light yellow crystals (70 mg, 59%). ^1H NMR d 1.31 (d, 12H), 1.70 (s, 4H), 2.34 (s, 3H), 6.88 (s, 1H), 7.17 (s, 1H), 8.03 (d, J = 8.4 Hz, 2H), 8.23 (d, J = 8.4 Hz, 2H), 8.45 (s, 1H)

N-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl)-2-naphthalenyl 4-ethoxycarbonyl benzaldimine (**Compound 4**)

A solution of 2-amino-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene (**Compound 20**, 0.088 g, 0.43 mmol) and ethyl 4-carboxybenzoate (**Compound 28** 0.077 g, 0.43 mmol) in CH_2Cl_2 (3.0 ml) was stirred at room temperature in the presence of $MgSO_4$ for 12 h. After concentration, the reaction mixture was purified by flash column chromatography (silica gel, 10% ethyl acetate in hexane) to yield yellow solids. These were recrystallized from 10% ethyl acetate in hexane to give the title compound as pale yellow crystals (0.081 g, 52%). ^1H NMR d 1.32 (d, 12H), 1.43 (t, J = 7.2 Hz, 3H), 4.42 (q, J = 7.1 Hz, 2H), 7.04 (dd, J_1 = 2.3 Hz, J_2 = 8.4 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H), 8.14 (d, J = 8.2 Hz, 2H), 8.54 (s, 1H).

N-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl)-2-naphthalenyl 4-ethoxycarbonyl acetophenone imine (**Compound 5**)

A solution of 2-amino-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene (**Compound 20**, 0.137 g, 0.67 mmol) together with ethyl 4-carboxyacetophenone (**Compound 27**, 0.12 g, 0.67 mmol) in benzene (anh. 10.0 ml) was stirred under reflux for 12 h in the presence of molecular sieves. The solvent was evaporated under reduced pressure. Purification of the resulting yellow gummy mixture by flash column chromatography (silica gel, 20% ethyl acetate in hexane) yielded yellow solids. These were recrystallized from 10% ethyl acetate in hexane to give the title compound as pale yellow crystals (100 mg, 41%). ^1H NMR d 1.29 (d, J = 5.0 Hz, 12H), 1.43 (t, J = 7.1 Hz, 3H), 1.70 (s, 4H),

2.29 (s, 3H), 4.41 (q, J = 7.1 Hz, 2H), 6.59 (dd, J_1 = 2.2 Hz, J_2 = 8.2 Hz, 1H), 6.73 (d, J = 2.1 Hz, 1H), 7.28 (d, J = 8.7 Hz, 1H), 8.03 (d, J = 8.1 Hz, 2H), 8.11 (d, J = 8.5 Hz, 2H).

N-(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl)-2-naphthalenyl 4-ethoxycarbonyl benzaldimine (**Compound 6**)

A solution of 2-amino-5,6,7,8-tetrahydro-3,5,5,8,8-pentamethylnaphthalene (**Compound 21**, 0.040 g, 0.184 mmol) together with ethyl 4-carboxybenzoate (**Compound 28**, 0.033 g, 0.184 mmol) in CH_2Cl_2 (5.0 ml) was stirred at room temperature in the presence of $MgSO_4$ for 12 h. After concentration, the residue was purified by flash column chromatography (silica gel, 10% ethyl acetate in hexane) to yield the title compound as a yellow oil. (0.02 g, 30%). ^1H NMR d 1.31 (d, 12H), 1.43 (t, J = 7.2 Hz, 3H), 1.69 (s, 4H), 2.31 (s, 3H), 4.42 (q, J = 7.1 Hz, 2H), 6.87 (s, 1H), 7.16 (s, 1H), 7.99 (d, J = 8.4 Hz, 2H), 8.14 (d, J = 8.3 Hz, 2H), 8.43 (s, 1H).

Ethyl 6-(N-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl) 3-ethoxycarbonyl-pyridine-6-carboxaldehyde imine (**Compound 7**)

A solution of 2-amino-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene (**Compound 20**, 0.056g, 0.27 mmol) together with ethyl 6-carboxynicotinate (**Compound 30**, 0.048 g, 0.27 mmol) in CH_2Cl_2 (3.0 ml) was stirred at room temperature in the presence of $MgSO_4$ for 24 h. The reaction mixture was filtered through celite and the resulting clear yellow solution was concentrated under reduced pressure to give a yellow oil. Purification of this yellow oil by column chromatography (silica gel, 10% ethyl acetate in hexane) afforded the title compound as light yellow

solids (0.070 g,. 58%). ^{1}H NMR d 1.32 (d, 12H), 1.45 (t, J = 7.1 Hz, 3H), 1.71 (s, 4H), 4.46 (q, J = 7.2 Hz, 2H), 7.14 (dd, J_1 = 2.2 Hz, J_2 = 8.4 Hz, 1H), 7.32 (d, J = 2.2 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 8.30 (d, J = 8.3 Hz, 1H), 8.40 (dd, J_1 = 2.2 Hz, J_2 = 8.2 Hz, 1H), 8.71 (s, 1H), 9.30 (d, J = 2.2 Hz, 1H).

N-6-(N-Isopropyl-2-oxo-4,4-dimethyl)quinolinyl 4-ethoxycarbonyl benzaldimine (**Compound 8**)

A solution of N-isopropyl 4,4-dimethyl-2-oxo-6-aminoquinoline (**Compound 34**, 0.22 g, 0.95 mmol) together with 4-ethoxycarbonyl benzaldehyde (**Compound 28**, 0.169 g, 0.95 mmol) in CH_2Cl_2 (2.0 ml) was stirred at room temperature in the presence of $MgSO_4$ for 24 h. The reaction mixture was filtered through celite and the resulting clear yellow solution was concentrated under reduced pressure to give a yellow oil. Purification of this yellow oil by column chromatography (silica gel, 30% ethyl acetate in hexane) afforded the title compound as light yellow solids (0.255 g, 69%). ^{1}H NMR d 1.32(s, 6H), 1.43 (t, J = 7.1 Hz, 3H), 1.56 (d, J = 7.0 Hz, 6H), 2.45 (s, 2H), 4.42 (q, J = 7.2 Hz, 2H), 4.70-4.79 (m, 1H), 7.14 (dd, J_1 = 2.1 Hz, J_2 = 8.7 Hz, 1H), 7.18 (d, J = 8.6 Hz, 1H), 7.25 (d, J = 2.0 Hz, 1H), 7.98 (d, J = 8.3 Hz, 2H), 8.15 (d, J = 8.3 Hz, 2H), 8.55 (s, 1H).

N-(4'-Ethoxycarbonyl)phenyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-2-carboxaldehyde imine (**Compound 9**)

A solution of 5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene-2-carboxaldehyde (**Compound 22**, 0.156 g, 0.72 mmol) together with ethyl 4-aminobenzoate (**Compound 29**, 0.238 g, 1.44 mmol) in dry benzene (2.0 ml) was refluxed in the presence of molecular sieves

for a day and half. The solvent was evaporated under vacuum to give a yellow oil. Purification by flash column chromatography (silica gel, 10% ethyl acetate in hexane) yielded yellow solids which were further purified by recrystallization from CH_2Cl_2/hexane to yield the title compound as yellow needles. ^1H NMR d 1.34 (d, J = 8.6 Hz, 12H), 1.41 (t, J = 7.1 Hz, 3H), 1.72 (s, 4H), 4.39 (q, J = 7.0 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.2 Hz, 1H), 7.68 (dd, J_1 = 1.8 Hz, J_2 = 8.3 Hz, 1H), 7.83 (d, J = 1.7 Hz, 1H), 8.07 (d, J = 6.6 Hz, 2H), 8.38 (s, 1H).

N-(4'-Ethoxycarbonyl)phenyl 2,2,4,4-tetramethyl-chroman-6-carboxaldehyde imine (**Compound 10**)

A solution of ethyl 4-aminobenzoate (**Compound 29**, 0.057 g, 0.35 mmol) together with 2,2,4,4-tetramethyl 6-chroman aldehyde (**Compound 24**, 0.047 g, 0.216 mmol) in benzene (anh. 2.0 ml) was stirred under reflux for 12 h in the presence of molecular sieves. The solvent was evaporated under reduced pressure. Purification of the resulting yellow gummy mixture by flash column chromatography (silica gel, 20% ethyl acetate in hexane) yielded the title compound as yellow solids (0.066 g, 83%). ^1H NMR d 1.41 (t, J = 7.1 Hz, 3H), 1.41 (d, J = 8.2 Hz, 12H), 1.89 (s, 2H), 4.39 (q, J = 7.1 Hz, 2H), 6.89 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 8.5 Hz, 2H), 7.62 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 7.88 (d, J = 1.95 Hz, 1H), 8.07 (d, J = 8.6 Hz, 2H), 8.34 (s, 1H).

N-(4'-Ethoxycarbonyl)phenyl-2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl) naphthalene-2-carboxaldehyde imine (**Compound 11**)

A solution of 5,6,7,8-tetrahydro-3,5,5,8,8-pentamethylnaphthalene-2-carboxaldehyde (**Compound 23**,

0.15 g, 0.65 mmol) together with ethyl 4-aminobenzoate (**Compound 29**, 0.118 g, 0.72 mmol) in benzene (2.0 ml) was stirred under reflux in the presence of molecular sieves for 24 h. The reaction mixture was filtered through celite and the clear yellow solution was concentrated under reduced pressure to give a yellow oil. Purification of this yellow oil by column chromatography (silica gel, 10% ethyl acetate in hexane) afforded the title compound as a light yellow oil (0.136 g, 55%). ^{1}H NMR d 1.33 (d, 12H), 1.41 (t, J = 7.1 Hz, 3H), 1.70 (s, 4H), 2.53 (s, 3H), 4.39 (q, J = 7.2 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 7.17 (s, 1H), 8.00 (s, 1H), 8.07 (d, J = 8.6 Hz, 2H), 8.63 (s, 1H).

Analogous to the condensation reaction described above and illustrated in the foregoing specific examples, the following further exemplary compounds of the invention can be prepared:

N-(4,4-dimethyl-6-)chromanyl 4-methoxycarbonyl benzaldimine;

N-(4,4-dimethyl-6-)chromanyl 4-carboxy benzaldimine;

N-(4,4-dimethyl-6-)chromanyl 4-ethoxycarbonyl benzaldimine;

N-(4,4-dimethyl-7-)chromanyl 4-methoxycarbonyl benzaldimine;

N-(4,4-dimethyl-7-)chromanyl 4-carboxy benzaldimine;

N-(4,4-dimethyl-7-)chromanyl 4-ethoxycarbonyl benzaldimine;

N-(2,2,4,4-tetramethyl-6-)chromanyl 4-methoxycarbonyl benzaldimine;

N-(2,2,4,4-tetramethyl-6-)chromanyl 4-carboxy benzaldimine;

N-(2,2,4,4-tetramethyl-7-)chromanyl 4-methoxycarbonyl benzaldimine;

N-(2,2,4,4-tetramethyl-7-)chromanyl 4-carboxy benzaldimine;

N-(2,2,4,4-tetramethyl-7-)chromanyl 4-ethoxycarbonyl benzaldimine;

N-(4,4-dimethyl-6-)thiochromanyl 4-methoxycarbonyl benzaldimine;

N-(4,4-dimethyl-6-)thiochromanyl 4-carboxy benzaldimine;

N-(4,4-dimethyl-6-)thiochromanyl 4-ethoxycarbonyl benzaldimine;

N-(4,4-dimethyl-7-)thiochromanyl 4-methoxycarbonyl benzaldimine;

N-(4,4-dimethyl-7-)thiochromanyl 4-carboxy benzaldimine;

N-(4,4-dimethyl-7-)thiochromanyl 4-ethoxycarbonyl benzaldimine;

N-(2,2,4,4-tetramethyl-6-)thiochromanyl 4-methoxycarbonyl benzaldimine;

N-(2,2,4,4-tetramethyl-6-)thiochromanyl 4-ethoxycarbonyl benzaldimine;

N-(2,2,4,4-tetramethyl-6-)thiochromanyl 4-carboxy benzaldimine;

N-(2,2,4,4-tetramethyl-7-)thiochromanyl 4-methoxycarbonyl benzaldimine;

N-(2,2,4,4-tetramethyl-7-)thiochromanyl 4-carboxy benzaldimine;

N-(2,2,4,4-tetramethyl-7-)thiochromanyl 4-ethoxycarbonyl benzaldimine;

N-(4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl) 4-methoxycarbonyl benzaldimine;

N-(4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)

4-carboxy benzaldimine;

N-(4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)-4-ethoxycarbonyl benzaldimine;

N-(4,4-dimethyl-1,2,3,4-tetrahydroquinolin-7-yl)-4-methoxycarbonyl benzaldimine;

N-(4,4-dimethyl-1,2,3,4-tetrahydroquinolin-7-yl)-4-carboxy benzaldimine;

N-(4,4-dimethyl-1,2,3,4-tetrahydroquinolin-7-yl)-4-ethoxycarbonyl benzaldimine;

N-(2,2,4,4-tetramethyl-1,2,3,4-tetrahydroquinolin-6-yl)-4-methoxycarbonyl benzaldimine;

N-(2,2,4,4-tetramethyl-1,2,3,4-tetrahydroquinolin-6-yl)-4-ethoxycarbonyl benzaldimine;

N-(2,2,4,4-tetramethyl-1,2,3,4-tetrahydroquinolin-6-yl)-4-carboxy benzaldimine;

N-(2,2,4,4-tetramethyl-1,2,3,4-tetrahydroquinolin-7-yl)-4-methoxycarbonyl benzaldimine;

N-(2,2,4,4-tetramethyl-1,2,3,4-tetrahydroquinolin-7-yl)-4-carboxy benzaldimine;

N-(2,2,4,4-tetramethyl-1,2,3,4-tetrahydroquinolin-7-yl)-4-ethoxycarbonyl benzaldimine;

N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-)naphthalenyl 3-methoxycarbonyl thiophene-5-carboxaldehyde imine;

N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-)naphthalenyl 3-carboxy thiophene-5-carboxaldehyde imine;

N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-)naphthalenyl 3-ethoxycarbonyl thiophene-5-carboxaldehyde imine;

N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-)naphthalenyl 3-methoxycarbonyl thiophene-5-carboxaldehyde imine;

N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-)naphthalenyl 3-carboxy thiophene-5-carboxaldehyde imine;

N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-)naphthalenyl 3-ethoxycarbonyl thiophene-5-carboxaldehyde imine;

N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-)naphthalenyl 3-methoxycarbonyl furan-5-carboxaldehyde imine;

N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-)naphthalenyl 3-carboxy furan-5-carboxaldehyde imine;

N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-)naphthalenyl 3-ethoxycarbonyl furan-5-carboxaldehyde imine;

N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-)naphthalenyl 3-methoxycarbonyl furan-5-carboxaldehyde imine;

N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-)naphthalenyl 3-carboxy furan-5-carboxaldehyde imine;

N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-)naphthalenyl 3-ethoxycarbonyl furan-5-carboxaldehyde imine;

N-(4'-methoxycarbonyl)phenyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-2-carboxaldehyde imine;

N-(4'-carboxy)phenyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-2-carboxaldehyde imine;

N-(4'-methoxycarbonyl)phenyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-3-carboxaldehyde imine;

N-(4'-ethoxycarbonyl)phenyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-3-carboxaldehyde imine;

N-(4'-carboxy)phenyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-3-carboxaldehyde imine;

N-(4'-ethoxycarbonyl)phenyl

4,4-dimethyl-chroman-6-carboxaldehyde imine;

N-(4'-methoxycarbonyl)phenyl 4,4-dimethyl-chroman-6-carboxaldehyde imine;

N-(4'-carboxy)phenyl 4,4-dimethyl-chroman-6-carboxaldehyde imine;

N-(4'-ethoxycarbonyl)phenyl 4,4-dimethyl-chroman-7-carboxaldehyde imine;

N-(4'-methoxycarbonyl)phenyl 4,4-dimethyl-chroman-7-carboxaldehyde imine;

N-(4'-carboxy)phenyl 4,4-dimethyl-chroman-7-carboxaldehyde imine;

N-(4'-methoxycarbonyl)phenyl 2,2,4,4-tetramethyl-chroman-6-carboxaldehyde imine;

N-(4'-carboxy)phenyl 2,2,4,4-tetramethyl-chroman-6-carboxaldehyde imine;

N-(4'-ethoxycarbonyl)phenyl 2,2,4,4-tetramethyl-chroman-7-carboxaldehyde imine;

N-(4'-methoxycarbonyl)phenyl 2,2,4,4-tetramethyl-chroman-7-carboxaldehyde imine;

N-(4'-carboxy)phenyl 2,2,4,4-tetramethyl-chroman-7-carboxaldehyde imine;

N-(4'-ethoxycarbonyl)phenyl 4,4-dimethyl-thiochroman-6-carboxaldehyde imine;

N-(4'-methoxycarbonyl)phenyl 4,4-dimethyl-thiochroman-6-carboxaldehyde imine;

N-(4'-carboxy)phenyl 4,4-dimethyl-thiochroman-6-carboxaldehyde imine;

N-(4'-ethoxycarbonyl)phenyl 4,4-dimethyl-thiochroman-7-carboxaldehyde imine;

N-(4'-methoxycarbonyl)phenyl 4,4-dimethyl-thiochroman-7-carboxaldehyde imine;

N-(4'-carboxy)phenyl 4,4-dimethyl-thiochroman-7-carboxaldehyde imine;

N-(4'-ethoxycarbonyl)phenyl 2,2,4,4-tetramethyl-thiochroman-6-carboxaldehyde imine;

N-(4'-methoxycarbonyl)phenyl 2,2,4,4-tetramethyl-thiochroman-6-carboxaldehyde imine;

N-(4'-carboxy)phenyl 2,2,4,4-tetramethyl-thiochroman-6-carboxaldehyde imine;

N-(4'-ethoxycarbonyl)phenyl 2,2,4,4-tetramethyl-thiochroman-7-carboxaldehyde imine;

N-(4'-methoxycarbonyl)phenyl 2,2,4,4-tetramethyl-thiochroman-7-carboxaldehyde imine;

N-(4'-carboxy)phenyl 2,2,4,4-tetramethyl-thiochroman-7-carboxaldehyde imine;

N-(4'-ethoxycarbonyl)phenyl 4,4-dimethyl-1,2,3,4-tetrahydroquinoline-6-carboxaldehyde imine;

N-(4'-methoxycarbonyl)phenyl 4,4-dimethyl-1,2,3,4-tetrahydroquinoline-6-carboxaldehyde imine;

N-(4'-carboxy)phenyl 4,4-dimethyl-1,2,3,4-tetrahydroquinoline-6-carboxaldehyde imine;

N-(4'-ethoxycarbonyl)phenyl 4,4-dimethyl-1,2,3,4-tetrahydroquinoline-7-carboxaldehyde imine;

N-(4'-methoxycarbonyl)phenyl 4,4-dimethyl-1,2,3,4-tetrahydroquinoline-7-carboxaldehyde imine;

N-(4'-carboxy)phenyl 4,4-dimethyl-1,2,3,4-tetrahydroquinoline-7-carboxaldehyde imine;

N-(4'-ethoxycarbonyl)phenyl 2,2,4,4-tetramethyl-1,2,3,4-tetrahydroquinoline-6-carboxaldehyde imine;

N-(4'-methoxycarbonyl)phenyl 2,2,4,4-tetramethyl-1,2,3,4-tetrahydroquinoline-6-carboxaldehyde imine;

N-(4'-carboxy)phenyl 2,2,4,4-tetramethyl-1,2,3,4-tetrahydroquinoline-6-carboxaldehyde imine;

N-(4'-ethoxycarbonyl)phenyl 2,2,4,4-tetramethyl-1,2,3,4-tetrahydroquinoline-7-carboxaldehyde imine;

N-(4'-methoxycarbonyl)phenyl 2,2,4,4-tetramethyl-

1,2,3,4-tetrahydroquinoline-7-carboxaldehyde imine;

N-(4'-carboxy)phenyl 2,2,4,4-tetramethyl-1,2,3,4-tetrahydroquinoline-7-carboxaldehyde imine;

N-(4'-ethoxycarbonyl)-2-thienyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-2-carboxaldehyde imine;

N-(4'-methoxycarbonyl)-2-thienyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-2-carboxaldehyde imine;

N-(4'-carboxy)-2-thienyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-2-carboxaldehyde imine;

N-(5'-ethoxycarbonyl)-2-thienyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-2-carboxaldehyde imine;

N-(5'-methoxycarbonyl)-2-thienyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-2-carboxaldehyde imine;

N-(5'-carboxy)-2-thienyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-2-carboxaldehyde imine;

N-(4'-ethoxycarbonyl)-2-furyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-2-carboxaldehyde imine;

N-(4'-methoxycarbonyl)-2-furyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-2-carboxaldehyde imine;

N-(4'-carboxy)-2-furyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-2-carboxaldehyde imine;

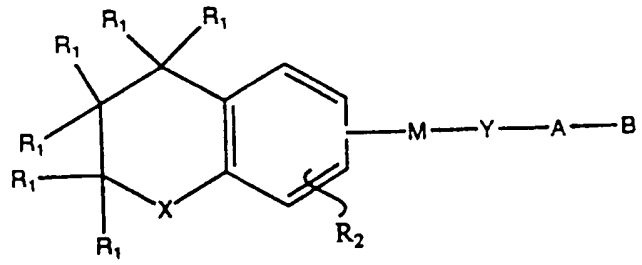
N-(5'-ethoxycarbonyl)-2-furyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-2-carboxaldehyde imine;

N-(5'-methoxycarbonyl)-2-furyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-2-carboxaldehyde imine;

N-(5'-carboxy)-2-furyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-2-carboxaldehyde imine.

WHAT IS CLAIMED IS

1. A compound of the formula



wherein the R_1 groups independently are hydrogen, lower alkyl of 1 to 6 carbons, or two geminal R_1 groups jointly represent an oxo (=O) or a thio (=S) group;

R_2 is hydrogen or lower alkyl of 1 to 6 carbons, or halogen;

M is $-N=CR_4-$ or $-R_4C=N-$ where R_4 is hydrogen or lower alkyl of 1 - 6 carbons;

X is $C(R_1)_2$, O, S, or NR_1;

Y is a phenyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pirimidinyl, pyrazinyl, thiazolyl, imidazolyl and oxazolyl, said phenyl group or said heteroaryl groups being optionally substituted with an R_3 group which is lower alkyl of 1 to 6 carbons or halogen;

A is $(CH_2)_n$ where n is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$,

$CR_7(OR_{12})_2$, or $CR_7OR_{13}O$, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons.

2. A compound of Claim 1 where the M group represents $-N=CR_4-$.

3. A compound of Claim 1 where the M group represents $-R_4C=N-$.

4. A compound of Claim 1 where Y is selected from the group consisting of phenyl, pyridyl, thienyl and furyl.

5. A compound of Claim 1 where X is $C(R_1)_2$.

6. A compound of Claim 1 where X is O.

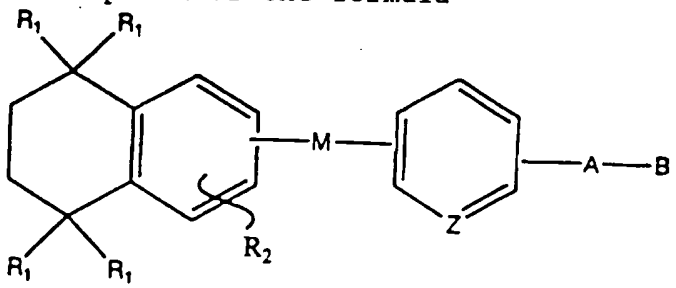
7. A compound of Claim 1 where X is S.

8. A compound of Claim 1 where X is NR_1.

9. A compound of Claim 1 where A is $(CH_2)_n$ and n is 0 to 3.

10. A compound of Claim 1 where B is COOH, or a pharmaceutically acceptable salt thereof, $COOR_8$ or $CONR_9R_{10}$.

11. A compound of the formula



wherein the R_1 groups independently are hydrogen, lower alkyl of 1 to 6 carbons;

R_2 is hydrogen or lower alkyl of 1 to 6 carbons, or halogen;

M is or $-N=CR_4-$ or $-R_4C=N-$ where R_4 is hydrogen or lower alkyl of 1 - 6 carbons;

Z is CH or N;

A is $(CH_2)_n$ where n is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, or $CR_7OR_{13}O$, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons.

12. A compound of Claim 11 where M is $-N=CR_4$.

13. A compound of Claim 12 where Z is N.

14. A compound of Claim 13 where the $-N=CR_4$ group is attached to the 2 position of the tetrahydronaphthalene ring and to the 2 position of the pyridine ring.

15. A compound of Claim 14 where the R_1 groups are CH_3, R_2 is H or CH_3, R_4 is H, A is $(CH_2)_n$, n is 0,

and B is COOH, a pharmaceutically acceptable salt thereof, $COOCH_3$ or $COOC_2H_5$.

16. A compound of Claim 15 where R_2 is H, and B is $COOC_2H_5$, and the $COOC_2H_5$ group is attached to the 5-position of the pyridine ring.

17. A compound of Claim 12 where Z is CH.

18. A compound of Claim 17 where the R_1 groups are CH_3, R_2 is H or CH_3, R_4 is H or CH_3, A is $(CH_2)_n$, n is 0, and B is COOH, a pharmaceutically acceptable salt thereof, $COOCH_3$ or $COOC_2H_5$.

19. A compound of Claim 18 where the $-N=CR_4$ group is attached to the 2 position of the tetrahydronaphthalene ring and the phenyl ring is 1,4 (para) substituted.

20. A compound of Claim 19 which is selected from the group consisting of:

N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl)-2-naphthalenyl 4-methoxycarbonyl benzaldimine,

N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl)-2-naphthalenyl 4-carboxy benzaldimine;

N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl)-2-naphthalenyl 4-carboxy benzaldimine,

N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl)-2-naphthalenyl 4-ethoxycarbonyl benzaldimine,

N-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl)-2-naphthalenyl 4-ethoxycarbonyl acetophenone imine, and

N-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl)-2-naphthalenyl 4-ethoxycarbonyl benzaldimine.

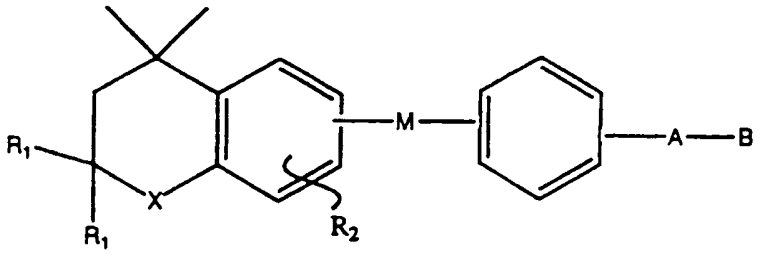
21. A compound of Claim 11 where M is $-CR_4=N-$.

22. A compound of Claim 21 where the R_1 groups are CH_3, R_2 is H or CH_3, R_4 is H or CH_3, A is $(CH_2)_n$, n is 0, and B is COOH, a pharmaceutically acceptable salt thereof, $COOCH_3$ or $COOC_2H_5$.

23. A compound of Claim 22 where Z is CH_1 the $-CR_4=N-$ is attached to the 2-position of the tetrahydronaphthalene ring and where the phenyl ring is 1,4 (para) substituted.

24. A compound of Claim 23 which is N-(4'-ethoxycarbonyl)phenyl 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-naphthalene-2-carboxaldehyde imine or N-(4'-ethoxycarbonyl)phenyl-2-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl) naphthalene-2-carboxaldehyde imine.

25. A compound of the formula



wherein the R_1 groups independently are hydrogen, lower alkyl of 1 to 6 carbons, or two geminal R_1 groups jointly represent an oxo (=O) group;

R_2 is hydrogen or lower alkyl of 1 to 6 carbons, or halogen;

M is or $-N=CR_4-$ or $-R_4C=N-$ where R_4 is hydrogen or lower alkyl of 1 - 6 carbons;

X is O or NR_1;

A is $(CH_2)_n$ where n is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, alkynyl having 2-6 carbons and 1 or 2 triple

bonds, and

B is hydrogen, COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11}, CH_2OCOR_{11}, CHO, $CH(OR_{12})_2$, $CHOR_{13}O$, $-COR_7$, $CR_7(OR_{12})_2$, or $CR_7OR_{13}O$, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl or lower alkylphenyl, R_{11} is lower alkyl, phenyl or lower alkylphenyl, R_{12} is lower alkyl, and R_{13} is divalent alkyl radical of 2-5 carbons.

26. A compound of Claim 25 where M represents $-R_4C=N-$.

27. A compound of Claim 26 where the $-R_4C=N-$ group is attached to the 6-position of the condensed heterocyclic ring and where the phenyl ring is 1,4 (para) substituted.

28. A compound of Claim 27 where X is O, the R_1 groups are CH_3, R_4 is H or CH_3, A is $(CH_2)_n$, n is 0, and B is COOH, a pharmaceutically acceptable salt thereof, $COOCH_3$ or $COOC_2H_5$.

29. A compound of Claim 28 which is N-(4'-ethoxycarbonyl)phenyl 2,2,4,4-tetramethyl-chroman-6-carboxaldehyde imine.

30. A compound of Claim 25 where M represents $-N=CR_4-$.

31. A compound of Claim 30 where X is NR_1, the $-N=CR_4-$ group is attached to the 6-position of the condensed heterocyclic ring and where the phenyl ring is 1,4 (para) substituted.

32. A compound of Claim 31 where the R_1 groups jointly represent an oxo group (=O), R_4 is H or methyl, A is $(CH_2)_n$, n is 0, and B is COOH, a pharmaceutically acceptable salt thereof, $COOCH_3$ or $COOC_2H_5$.

33. A compound of Claim 32 which is N-6-(N-isopropyl-2-oxo-4,4-dimethyl)quinolinyl 4-ethoxycarbonyl benzaldimine.

INTERNATIONAL SEARCH REPORT

Interna' ' Application No
PCT/US 95/10802

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C251/24 C07D213/80 C07D215/38 C07D311/58 C07D311/70
C07D335/06 C07D333/38 C07D307/68 C07D215/12 A61K31/19
A61K31/47 A61K31/38 A61K31/35 A61K31/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 514 269 (CIRD GALDERMA) 19 November 1992 see page 8, line 3 - line 34; claims ---	1-5,9-24
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
30 November 1995	11 -12- 1995

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Seufert, G

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INTERNATIONAL SEARCH REPORT

Interna' Application No
PCT/US 95/10802

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	'CAS Registry Handbook 1988' , AMERICAN CHEMICAL SOCIETY see RN 116496-95-8, 116496-57-2 ---	1,3-5,9
A	WO,A,93 06086 (PFIZER INC.) 1 April 1993 see page 9, line 29 - page 10, line 29; claims; examples ---	1-32
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A	US,A,4 980 369 (R. A. S. CHANDRARATNA) 25 December 1990 cited in the application see column 1, line 51 - column 59; claims; examples ---	1-32
A	US,A,5 089 509 (R. A. S. CHANDRARATNA) 18 February 1992 cited in the application see column 1, line 50 - line 59; claims; examples ---	1-32

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INTERNATIONAL SEARCH REPORT

Interna[illegible]l Application No
PCT/US 95/10802

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US,A,5 006 550 (R. A. S. CHANDRARATNA) 9 April 1991 cited in the application see column 1, line 60 - line 68; claims; examples -----	1-32

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PCT/US 95/10802

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